223. **(Amended)** An isolated polypeptide of any one of claims 202-203 comprising at least about 50 consecutive amino acid residues of SEQ ID NO:764.

224. **(Amended)** An isolated polypeptide of any one of claims 202-203 comprising at least about 100 consecutive amino acid residues of SEQ ID NO:764.

REMARKS

Claims 113-120, 123-125, 127-135, 149-150, and 196-224 were pending in the application. Claims 113-120, 124-131, 134, 135, 150, 196-201, 204-211, and 213-219 have been canceled, without prejudice, and claims 123, 132, 133, 149, 220-224 have been amended. Accordingly, claims 123, 132, 133, 149, 202, 203, 212, and 220-224 will be pending in the instant application after the amendments presented herein have been entered. For the Examiner's convenience, the claims that will be pending in the application upon entry of the instant Amendment are set forth in Appendix A. *No new matter has been added.*

Applicant submits herewith a "**Version with Markings to Show Changes Made**," which indicates the specific amendments made to the specification and the claims.

Any amendments to and/or cancellation of the claims is not to be construed as an acquiescence to any of the rejections set forth in the instant Final Office Action, and was done solely to expedite prosecution of the application. Applicant hereby reserves the right to pursue the subject matter of the claims as originally filed in this or a separate application(s).

Rejection of Claims 113-120, 123-125, 127-135, 149-150, 196-213, and 213-224 Under 35 U.S.C. §101

The Examiner has maintained the rejection of claims 113-120, 123-125, 127-135, 149-150, 196-213, and 213-224 Under 35 U.S.C. §101 "because the claimed invention is not supported by either a specific and substantial, a credible asserted utility, or a well established utility. In particular, the Examiner is of the opinion that

> A representative number of species for the claimed genus of polypeptides has not been described, not enabled as a diagnostic or vaccine polypeptide[s]. Just because a polypeptide is defined as a surface polypeptide, does not automatically define the polypeptide as a diagnostic or vaccine antigen. Even if the claimed invention were limited to just SEQ ID NO 764, the asserted biological activity of a polypeptide molecule is not defined by a linear sequence of amino acids.

Furthermore, the Examiner is of the opinion that

> [t]he cited references, Doig, et al (1995) and [Bina] et al (2000), supplied by Applicant, compare SEQ ID NO 764 to the protein of [Bina] et al, which has been 'shown to be antigenic in vivo with both patient sera and specific monoclonal antibodies'. It is clear to the examiner that the antigen of [Bina] induces antibodies, these antibodies are present in patients that are still sick. The antibodies induced in vivo are not protective antibodies because infection persists. The protein of [Bina] has 250 amino acids and functions as a porin. The claimed polypeptide of SEQ ID No 764 only has 170 amino acids and no credible asserted utility. The protein of [Bina] is not defined as the same polypeptide of the instantly claimed invention, but is argues to 'correspond substantially'. The instant specification does not define SEQ ID No 764 as corresponding substantially to the protein of [Bina]. The meaning of the phrase 'corresponds substantially', with respect to SEQ ID No 764, has not been defined [in] the instant specification. The polypeptide of the invention is argued to be immunogenic and could induce antibodies which in turn could be used to identify the polypeptide, how circular reasoning defines a substantial, credible or well established utility has not been established.

Claims 113-120, 123-125, 127-135, 149-150, 196-213, and 213-224 also stand rejected under 35 U.S.C. §112, first paragraph, as, according to the Examiner, "containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention."

Applicant respectfully traverses the foregoing rejections. Applicant respectfully submits that claims 113-120, 124-131, 134, 135, 150, 196-201, 204-211, and 213-219 have been canceled, thus rendering the foregoing rejection moot as it pertains to these claims. Claims 202 and 203, and claims dependent therefrom, remain pending. Claim 202 is drawn to an isolated polypeptide comprising at least 10 consecutive amino acid residues of SEQ ID NO: 764, wherein said polypeptide comprises at least one epitope recognized by a T cell receptor specific for the polypeptide set forth in SEQ ID NO:764. Claim 203 is directed to an isolated polypeptide comprising at least 10 consecutive amino acid residues of SEQ ID NO: 764, wherein said polypeptide comprises at least one antigenic determinant of the polypeptide set forth in SEQ ID NO:764. Claim 123 is directed to an isolated polypeptide of any one of claims 202-203 which is a recombinant polypeptide. Claim 132 is directed to a fusion protein comprising a polypeptide of any one of claims 202-203 and an additional amino acid sequence. Claim 133 is directed to a fusion protein of claim 132, wherein the additional amino acid sequence comprises an *H. pylori* polypeptide. Claim 149 is directed to a composition comprising a polypeptide of any one of claims 202-203 and a pharmaceutically acceptable carrier. Claim 212 is directed to a composition comprising a fusion protein of claim 132 and a pharmaceutically acceptable carrier. Claims 220, 221, 222, 223, and 224 are directed to an isolated polypeptide of any one of claims

202-203 comprising at least about 12, 16, 20, 50, or 100 consecutive amino acid residues of SEQ ID NO:764, respectively.

The present invention features a novel surface protein from the bacteria *Helicobacter pylori*. Applicant has described the chemical, physical, and biological properties of the polypeptide set forth as SEQ ID NO: 764. As set forth in the Amendment and Response to the previous Office Action (Paper No. 29) and reiterated herein, Applicant asserts that the polypeptides of the invention ***can be used for diagnostic and therapeutic purposes with regard to H. pylori infection; for generating antibodies; and to evaluate compounds useful as activators or inhibitors of the bacterial life cycle*** (see, for example, the specification at page 50). Applicant maintains that the proposed utilities are specific and substantial utilities and are also credible, and thus satisfy the requirements of 35 U.S.C. §101. As the Examiner is aware, "an applicant need only make one credible assertion of specific utility for the claimed invention to satisfy §101 and §112." *Utility Guidelines*, page 15. A credible utility is assessed by ascertaining "whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of the evidence and reasoning provided." *Utility Guidelines*, page 17.

The specificity of the asserted utilities is based on the fact that the polypeptide set forth as SEQ ID NO:764 is a surface protein of the *H. pylori* pathogen, and, as such, is an attractive target for intervention. The significant pathologies attributed to *H. pylori* infection (*e.g.*, gastritis, peptic ulceration, gastric cancer) have made effective diagnosis, treatment and prevention desirable. Accordingly, Applicant asserts that the claimed polypeptides possess a specific and credible utility, as all polypeptides are not capable of utility for diagnostics and therapeutics for *H. pylori*.

As further evidence of the asserted utilities as set forth above, Applicant submits herewith, as Appendix B, the Declaration of Dr. Peter C. Doig Pursuant to 37 C.F.R. §1.132 (hereinafter "the Declaration"). The Declaration presents the results of experiments that ***corroborate the asserted utilities of the claimed invention as were originally disclosed in the instant application.***

An applicant can rebut an Examiner's rejection under 35 U.S.C. §101 using any one of the following: amendments to the claims, arguments or reasoning, ***or new evidence submitted in a Declaration under 37 C.F.R. §1.132***, or in a printed publication (*see* page 18 of the *Utility Guidelines*). The Declaration describes experiments which confirm that the claimed polypeptides, *e.g.*, SEQ ID NO:764 and fragments of at least 10 amino acids, have the ability to induce an immune response.

As set forth in the Declaration, monoclonal antibodies were produced using recombinant his-tagged HopE (full length mature sequence –11 C-terminal amino acids). The amino acid sequence of HopE used in the experiments is identical to the amino acid sequence of SEQ ID NO:764 at residues 24 through 155 of SEQ ID NO:764. Peptides were synthesized as 10-mers with an 8-amino acid overlap, with the first peptide starting at the glutamic acid residue of the mature, process protein and ELISA was performed. Mimitope analysis was able to map the epitopes of all monoclonal antibodies examined. The primary peptides that reacted with either monoclonal or polyclonal sera are shown in Table 1 of the Declaration. These peptides are present within the amino acid sequence of SEQ ID NO:764 as described in the specification, as illustrated by the amino acid sequence of SEQ ID NO:764 shown as Appendix C, attached

hereto. The location of each epitope is identified by bold, or italicized font, underlining, or double underlining within the sequence of SEQ ID NO:764.

Contrary to the Examiner's assertion that it is "circular reasoning" to say that the claimed polypeptides induce antibodies which in turn could be used to identify the polypeptide, Applicant respectfully submits that the immunogenicity of the claimed polypeptides, as evidenced by the results of the experiments set forth in the Declaration, supports the asserted utility of SEQ ID NO:764, and fragments thereof, as having utility as diagnostics and therapeutics with regard to *H. pylori* infection.

The Examiner is further of the opinion that

> [u]pon consideration of the arguments and the references submitted by Applicant, the examiner believes that evidence has been made of record that defines portions of SEQ ID NO 764 to evidence antigenic cross reactivity with the P2 porin of Haemophilus pathogen. The existence of cross reactive epitopes would induce cross reactive antibodies which would result in a false positive diagnostic result. Therefore, Applicant has made of record arguments and evidence that polypeptides of SEQ ID No 764 would not serve as a diagnostic polypeptide for H. pylori infection due to the existence of conserved portions of SEQ ID NO 764 being shared with H. influenzae, both are human pathogens. With respect to arguments made regarding evidence to how that SEQ ID No 764 is not a vaccine antigen, the examiner would like to point out the fact that Roupouli et al (1993) and HP World Wide (1991) documents have previously been made of record which show that H. pylori vaccines are in the developmental stages and are not predictable. HP World Wide cited Dunkley and Heap who found H. pylori compositions did not induce protective immunity. No showing has been made of record that indicates that the conserved portions of the H. influenza P2 porin are those portions responsible for the induction of protective immune response against Helicobacter pylori as well. Therefore, arguments that H. influenza P2 protein and Helicobacter polypeptide SEQ ID No 764 are both protective antigens are not convincing.

Applicant respectfully submits that Heap, Dunkley, and Monath do not teach that the administration of *H. pylori* antigens provide no protection. To the contrary, they claim that only gastrointestinal routes may not be effective for stimulation of protective immune response.

Moreover, with respect to the use of the polypeptides of the instant invention as a diagnostic, Applicant respectfully submits that the references submitted by Applicant (Doig *et al.* (1995) *J. Bacteriology 177:5447*, and Bains *et al* (2000) *J. Bacteriology* 182:2370) and arguments presented in the response to the previous Office Action (Paper No. 29), ***do not*** define "portions of SEQ ID NO 764 to evidence antigenic cross reactivity with the P2 porin of Haemophilus pathogen" as stated by the Examiner. Applicant reiterates the comments set forth in the response to the previous Office Action (Paper No. 29) as follows.

> each of these publications describes members of the HOP family of molecules, bacterial porin proteins which are know[n] to share chemical, physical and biological properties....a member of this family, HopE (to which SEQ ID NO:764 corresponds substantially), has been shown to be antigenic *in vivo* as assessed by sera taken from *H. pylori*-infected individuals, and is immunologically conserved with both patient sera and specific monoclonal antibodies.

As set forth above and in the Declaration, HopE and SEQ ID NO:764 are identical over amino acids 24 through 155 of SEQ ID NO:764.

Moreover, in the previous response, Applicant made the statement that "porins, including the P2 porin of *H. influenzae*, have been used as immunogens that are actively and/or passively protective in subsequent challenge experiments" to illustrate that porins have been used as protective immunogens.

As stated by the Examiner, "comparison of SEQ ID NO 764 with Haemophilus influenzae porin protein P2 (U.S. Pat. 6,153,406) shows SEQ ID NO 764 (170 amino acids)

shares **43 amino acids** with SEQ ID NO 10 (342 amino acids)." Applicant respectfully submits that porin P2 and SEQ ID NO:764 **do not share more than 2 *consecutive* amino acids.** Moreover, as evidenced by the Declaration, monoclonal antibodies have been identified which are ***specific to SEQ ID NO:764.*** It is Applicant's position that the Examiner has not provided evidence of the existence of cross reactive epitopes which would induce cross reactive antibodies resulting in a false positive diagnostic result.

As the Examiner is aware, the Applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond reasonable doubt." *In re Irons*, 340 F.2d 974, 978, 144 USPQ 351, 354 (CCPA 1965). Instead, evidence will be sufficient, if considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. §2164.07. In view of all the foregoing, it is evident that Applicant's invention has a *specific, substantial, and credible utility* that would have been readily apparent to one of skill in the art. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the foregoing 35 U.S.C. §101 and §112, first paragraph rejections.

Rejection of Claims 113-120, 123, 125-131 132-133, 134-135, 149, 196-201, 204, 205-212, 214-219, 220-224 Under 35 U.S.C. §112, first paragraph

The Examiner has maintained the rejection of claims 113-120, 123, 125-131 132-133, 134-135, 149, 196-201, 204, 205-212, 214-219, 220-224 under 35 U.S.C. §112, first paragraph, "as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the

application was filed, had possession of the claimed invention for reasons of record on paper number 26."

With respect to claims 113-120, 123, 132-133, 149, and 196-201, the Examiner is of the opinion that "while the instant specification suggests polypeptides of the recited structural components held in common with SEQ ID NO:764, no structural polypeptides of the same functional characteristics of SEQ ID NO:764 have been described."

At page 11 of the instant Office Action, the Examiner applies the instant 35 U.S.C. §112, first paragraph rejection to claims 125-131 and 134-135. Although claims 125, 127, 128, 129, 130, 131, 134, and 135 were not included in the "Rejections Maintained" section of the instant Office Action, Applicant assumes these claims were intended to be included in the rejection based on their inclusion on page 11 of the Office Action.

With respect to claims 125-131 and 134-135, the Examiner is of the opinion that "the claims is described for Helicobacter polypeptides up to 170 amino acids that are encoded by SEQ ID No 764. Helicobacter polypeptides larger than 170 amino acids and comprise SEQ ID NO 764 do not evidence original descriptive support."

Applicant respectfully traverses the foregoing rejections. However, while in no way acquiescing to the Examiner's rejections, Applicant has canceled claims 113-120, 125-131, 134, 135, 150, 196-201, 204-211, and 213-219, and has amended claims 123, 132, 133, 149, 220, 221, 222, 223, and 224 so that they are no longer dependent on the canceled claims, thereby rendering the foregoing rejection moot.

CONCLUSION

In view of the foregoing amendments and remarks, reconsideration of the rejections and allowance of all pending claims are respectfully requested. If a telephone conversation with Applicant's Attorney would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

Respectfully submitted,

Amy E. Mandragouras, Esq
Reg. No. 36,207
Attorney for Applicant

LAHIVE & COCKFIELD, LLP
28 State Street
Boston, MA 02109
(617) 227-7400
Dated: March 4, 2002

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 113-120, 124-131, 134, 135, 150, 196-201, 204-211, and 213-219, have been canceled, without prejudice, and claims 123, 132, 133, 149, 220, 221, 222, 223, and 224 have been amended as follows:

123. **(Amended)** An isolated polypeptide of any one of claims ~~196-204~~ 202-203 which is a recombinant polypeptide.

132. **(Amended)** A fusion protein comprising a polypeptide of any one of claims ~~113, 120 or 196-204~~ 202-203 and an additional amino acid sequence.

133. **(Amended)** ~~The~~ A fusion protein of claim 132, wherein the additional amino acid sequence comprises an *H. pylori* polypeptide.

149. **(Amended)** A composition comprising a polypeptide of any one of claims ~~113, 120 or 196-204~~ 202-203 and a pharmaceutically acceptable carrier.

220. **(Amended)** ~~The~~ An isolated polypeptide of any one of claims 202-~~204~~ 203 comprising at least about 12 consecutive amino acid residues of SEQ ID NO:764.

221. **(Amended)** ~~The~~ An isolated polypeptide of any one of claims 202-~~204~~ 203 comprising at least about 16 consecutive amino acid residues of SEQ ID NO:764.

222. **(Amended)** ~~The~~ An isolated polypeptide of any one of claims 202-~~204~~ 203 comprising at least about 20 consecutive amino acid residues of SEQ ID NO: 764.

223. **(Amended)** ~~The~~ An isolated polypeptide of any one of claims 202-~~204~~ 203 comprising at least about 50 consecutive amino acid residues of SEQ ID NO:764.

224. **(Amended)** ~~The~~ An isolated polypeptide of any one of claims 202-~~204~~ 203 comprising at least about 100 consecutive amino acid residues of SEQ ID NO:764.